Management of Human Immunodeficiency Virus–Infected Pregnant Women at Latin American and Caribbean Sites

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OBJECTIVE: To describe the management of a population of human immunodeficiency virus (HIV)–infected pregnant women in Latin America and the Caribbean, and to assess factors associated with maternal viral load of 1,000 copies/mL or more and with infant HIV-1 infection.

METHODS: Eligibility criteria were enrollment in the prospective cohort study as of March 2006; delivery of a liveborn, singleton infant; and completion of the 6-month postpartum or postnatal visit.

RESULTS: Of 955 women enrolled in Argentina, the Bahamas, Brazil, and Mexico, 770 mother-infant pairs were eligible. At enrollment, most women were relatively healthy (87% asymptomatic, 59% with viral load less than 1,000 copies/mL, 62% with CD4$^+$% of 25% or more). Most (99%) received antiretrovirals during pregnancy (56% prophylaxis, 44% treatment), and 38% delivered by cesarean before labor and before ruptured membranes. Only 18% of women had a viral load of 1,000 copies/mL or more after delivery (associated in adjusted analyses with receipt of antiretrovirals at conception, CD4$^+$% [lower], viral load [higher], and country at enrollment, enrollment late in pregnancy, and inversely related to antiretroviral regimen [two nucleoside or nucleotide analogue reverse transcriptase inhibitors plus one nonnucleoside reverse transcriptase inhibitor] during pregnancy). None of the infants breastfed, and all received antiretroviral prophylaxis. Seven infants became infected (0.91%; 95% confidence interval 0.37–1.86). Low birth weight infants and those whose mothers had a low CD4$^+$% at hospital discharge after delivery and were not receiving antiretrovirals at enrollment were at higher risk of HIV infection.

CONCLUSION: Only a minority of women had a viral load of 1,000 copies/mL or more around delivery, and mother-to-child transmission of HIV occurred rarely (1%).

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LEVEL OF EVIDENCE: II

Millions of women around the world have become infected with the human immunodeficiency virus type 1 (HIV) over the past two decades, and the great majority of HIV-infected children in the United States and elsewhere acquire the infection from their mothers.[1] Major progress has been made in the medical management of HIV-infected pregnant women and in the prevention of mother-to-child transmission of HIV in the United States and Europe.[2] Little information has been published regarding the medical management of HIV-infected women in other settings, including Latin America and the Caribbean, where effective interventions to improve the health of HIV-infected women during pregnancy and to prevent mother-to-child transmission of HIV are feasible. Objectives of the current analysis included describing the management of HIV-infected pregnant women receiving care at clinical centers in Latin America and the Caribbean participating in the National Institute of Child Health and Human Devel-

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opment (NICHD) International Site Development Initiative (NISDI) Perinatal Study, and determining factors associated with two outcomes: a maternal plasma HIV RNA concentration (viral load) of 1,000 copies/mL or more around the time of delivery, and mother-to-child transmission of HIV. Another objective was to describe the NICHD International Site Development Initiative Perinatal Study's design and methodology.

MATERIALS AND METHODS

The NICHD International Site Development Initiative Perinatal Study is a prospective cohort study conducted in Latin America and Caribbean countries. The primary objectives of this observational study include describing the characteristics of HIV-infected pregnant women and their HIV-exposed infants, including the use of interventions for prevention of mother-to-child transmission of HIV (antiretroviral prophylaxis, cesarean delivery before labor and before ruptured membranes [elective cesarean delivery], and complete avoidance of breastfeeding); the receipt of antiretrovirals or other therapy for the woman's own health; and rates of mother-to-child transmission of HIV. Enrollment began in September 2002 and is ongoing. Women are eligible for enrollment if their pregnancy is confirmed, their HIV infection is documented, they intend to deliver at a participating clinical site and to be followed up for 6 months (along with the infant) after delivery or birth, and they are willing and able to provide informed consent. Enrollment has to occur before delivery. Signed informed consent is obtained for all subjects before enrollment into the study. The protocol was approved by the ethical review board at each clinical site where subjects were enrolled, as well as by institutional review boards at the sponsoring institution and at the data management center (Westat).

Maternal study visits were conducted during pregnancy, at delivery, at hospital discharge after delivery, and after delivery (at 6–12 weeks and 6 months postpartum). Infant study visits were conducted before hospital discharge after birth, at 6–12 weeks, and at 6 months. During each of these study visits, a medical history was obtained, a physical examination was conducted, and laboratory samples were obtained (except at the delivery and the 6-month postpartum visits for mothers).

Clinical, immunologic, and virologic characteristics of the women are assessed during pregnancy, at the time of hospital discharge after delivery, and at the 6–12 week postpartum visit. Maternal clinical disease staging is performed with the use of the 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for acquired immunodeficiency syndrome (AIDS) among adolescents and adults[3] at each study visit. A maternal history of substance use during the index pregnancy is ascertained through maternal interview at enrollment.

Infants are categorized as HIV-infected if they have any two of the following (obtained from separate specimens): positive HIV culture, positive HIV DNA polymerase chain reaction assay, positive neutralizable HIV p24 antigen assay, or plasma HIV RNA concentration more than 1,000 copies/mL. Infants are considered HIV-uninfected if they have two or more negative HIV virologic assays (eg, HIV culture or HIV DNA polymerase chain reaction), with one test performed at age 1 month or older and one performed at age 4 months or older, and no positive virologic tests. Alternatively, infants also are considered HIV-uninfected if they have one positive HIV virologic assay with at least two subsequent negative HIV virologic tests, with at least one performed after age 4 months, or if they have two negative HIV antibody test results, with at least one being performed after age 6 months.

The study population for this analysis was restricted to women enrolled in the NICHD International Site Development Initiative Perinatal Study as of March 2006, who delivered liveborn, singleton infants and who, along with their infants, completed follow-up on study through the 6-month postpartum and postnatal visits. Homemakers, unemployed individuals, and students were classified as not gainfully employed outside of the home; all others were classified as gainfully employed outside of the home. Maternal nutritional status at enrollment was characterized according to body mass index (BMI) adjusted for length of gestation using an algorithm available from the Ministry of Health of Argentina.[4] Parity was categorized as nulliparous (0), primiparous (1) and multiparous (2 or more). Mode of delivery was categorized as vaginal or cesarean delivery and, if cesarean, as elective cesarean delivery or as cesarean delivery after labor or after ruptured membranes (other cesarean delivery).

For those women who received one or more antiretrovirals during pregnancy, receipt of antiretrovirals was categorized as either prophylaxis or treatment. Women were classified as having received prophylaxis if they were not receiving antiretrovirals when they became pregnant, but they initiated one or more antiretrovirals during pregnancy and discontinued these drugs at or before the 6–12 week postpartum visit. Conversely, women were classified as receiving treatment if they were receiving antiretrovirals when they

became pregnant or continued antiretrovirals after the 6–12 week postpartum visit.

Antiretroviral regimens received during pregnancy for at least 28 days[5,6] were categorized according to complexity as follows (from least complex to most complex): one nucleoside or nucleotide analogue reverse transcriptase inhibitor only; two nucleoside or nucleotide analogue reverse transcriptase inhibitors; two nucleoside or nucleotide analogue reverse transcriptase inhibitors with one nonnucleoside reverse transcriptase inhibitor; and two nucleoside or nucleotide analogue reverse transcriptase inhibitors with one protease inhibitor. If two regimens of equal complexity were received for 28 days or more during pregnancy, the regimen received later in pregnancy took precedence over a regimen received earlier during pregnancy. Also, given that two regimens were received for 28 days or more, a longer duration did not alter the ordering of complexity of regimens as delineated above.

Low birth weight was defined as a birth weight of less than 2,500 g. Preterm infants were those with a gestational age at birth of less than 37 completed weeks. Infant gestational age at birth (in completed weeks) was determined either by obstetric estimation (dates of last menstrual period with or without ultrasonography) or by pediatric newborn examination (Ballard et al,[7] Dubowitz et al,[8] or Capurro et al[9]).

Statistical analysis was conducted using SAS 9.1 (SAS Institute Inc., Cary, NC). The Fisher exact test and the Fisher-Freeman-Halton test were used on all 2×2 and row×column tables comparing categorical variables.[10] Means of continuous variables between study groups were compared using unpaired *t* tests. Wilcoxon rank sum and Kruskal-Wallis analysis of variance tests were used to compare medians. $P=.05$ was considered to be significant. Variables at least marginally associated with outcome (at the 20% significance level) were considered candidates for the multivariable logistic regression modeling. For the logistic regression modeling, both stepwise selection and backward elimination strategies were applied to determine whether both selection procedures arrived at the same parsimonious model (using a 5% significance level).

RESULTS

As of March 2006, 955 women were enrolled in the International Site Development Initiative Perinatal Study at clinical sites in Argentina, the Bahamas, Brazil, and Mexico. The derivation of the study population of 770 mother-infant pairs is illustrated in Figure 1.

Characteristics of the 770 women in the study population are shown in Table 1. Most women were asymptomatic (Centers for Disease Control and Prevention Class A) (87%), with a viral load less than 1,000 copies/mL (59%) and with a $CD4^+$% of 25% or more (62%). Although most women (83%) were not

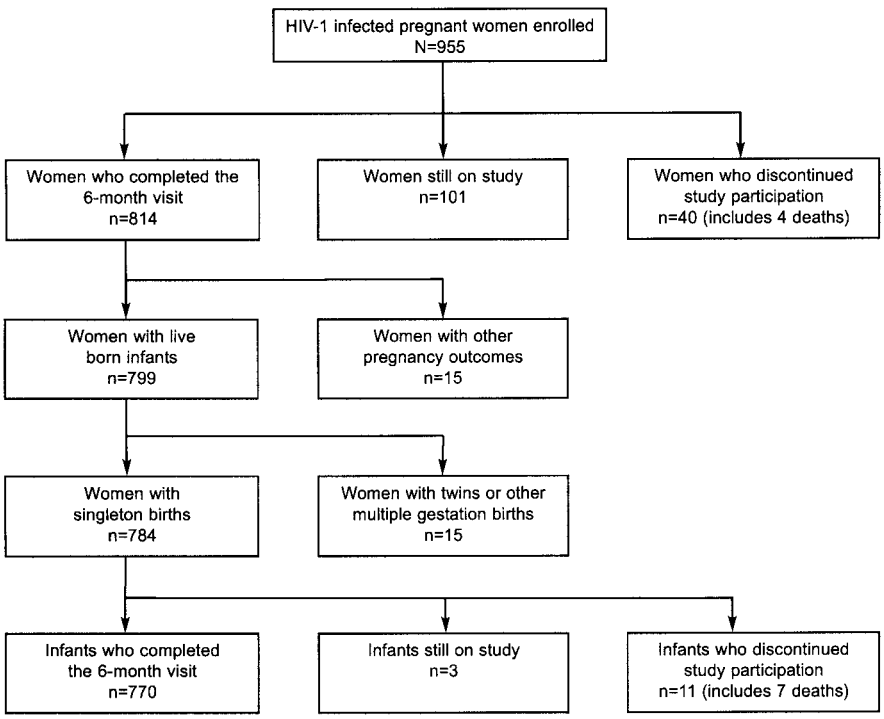

Fig. 1. Derivation of the study population. HIV, human immunodeficiency virus.

Read. Management of HIV-Infected Women. Obstet Gynecol 2007.

receiving antiretrovirals at conception, most (81%) were receiving antiretrovirals at enrollment into the NICHD International Site Development Initiative protocol. At enrollment, statistically significant differences according to country of residence were observed in terms of demographic characteristics (education, employment, and marital status), adjusted BMI, tobacco and cocaine use during pregnancy, parity, gestational age (trimester) at enrollment, HIV clinical classification, viral load, and receipt of antiretrovirals (whether receiving antiretrovirals at conception or at enrollment into the NICHD International Site Development Initiative study). The median gestational age at enrollment also varied significantly according to country of residence, from 22 weeks in Argentina to 33 weeks in Mexico (overall median 27 weeks) ($P<.001$) (data not shown). No statistically significant differences according to country were observed for maternal age (58% between 20–29 years), mode of acquisition of HIV infection (97% heterosexual), or alcohol (9%) and marijuana (2%) use during pregnancy.

During pregnancy, virtually all women (99%) received one or more antiretrovirals (56% prophylaxis, 44% treatment). However, among those who received antiretrovirals during pregnancy, there were significant differences according to country of residence in terms of the number of antiretroviral regimens received during pregnancy, the most complex antiretroviral regimen received during pregnancy, and the reason for receipt of antiretrovirals during pregnancy (prophylaxis compared with treatment).

The majority of women (59%) delivered by cesarean (elective cesarean delivery: 38%; other cesarean delivery 21%). The mode of delivery varied significantly according to country. Overall, the most common indications for elective cesarean delivery were prevention of mother-to-child transmission of HIV (n=134; 46%), repeat cesarean section (n=72; 25%), and nonreassuring fetal heart rate (n=13; 4%) Similarly, the most common indications for other cesarean delivery were prevention of mother-to-child transmission of HIV (n=49; 31%), prolonged rupture of membranes (n=22; 14%), and repeat cesarean delivery (n=17; 11%). Duration of ruptured membranes also varied significantly by country.

The median length of time between delivery and hospital discharge was 2 days, and this also differed according to country, ranging from 1 day in the Bahamas to 3 days in Argentina ($P<.001$) (data not shown). Although there were significant differences according to country in terms of HIV clinical classification and viral load at hospital discharge, $CD4^+$% at hospital discharge did not differ significantly according to country. At 6–12 weeks postpartum, HIV clinical classification varied by country, but viral load (44% had viral load less than 1,000 copies/mL) and $CD4^+$% (62% had $CD4^+$% of 25% or more) did not.

Because the timing of enrollment into the study varied significantly according to country of residence, characteristics of the women were further evaluated according to the timing of enrollment. Human immunodeficiency virus clinical classification ($P=.044$) and viral load ($P<.001$) at enrollment varied significantly according to the timing of enrollment, with women with more advanced HIV disease or with higher viral loads enrolled during the first or second trimester of pregnancy. Although most women (83%) were not receiving antiretrovirals at conception, the proportion not receiving antiretrovirals at conception was higher among those who enrolled later in pregnancy ($P<.001$). Conversely, although most women (81%) were receiving antiretrovirals at the time of enrollment, the proportion receiving antiretrovirals at enrollment was higher among those who enrolled later in pregnancy ($P<.001$). Although virtually all women (99%) received antiretrovirals during pregnancy, only 80% of those who enrolled at the delivery visit had received antiretrovirals during pregnancy ($P<.001$). Most women (78%) received only one antiretroviral regimen during pregnancy, but a greater proportion of those enrolled earlier in pregnancy received two or more regimens compared with those who enrolled later in pregnancy ($P<.001$). Although the most complex antiretroviral regimen received during pregnancy did not vary significantly according to the timing of enrollment, the reason for receipt did (most women enrolled in the first trimester received antiretrovirals for treatment, while most enrolled at the delivery visit received antiretrovirals for prophylaxis) ($P=.034$). The mode of delivery and duration of ruptured membranes did not differ significantly according to the timing of enrollment, nor did viral load or $CD4^+$% at hospital discharge after delivery. At 6–12 weeks postpartum, clinical classification, viral load, and CD4% did not vary significantly according to the timing of enrollment.

Women who received antiretrovirals during pregnancy for prophylaxis were more likely to be asymptomatic (Centers for Disease Control and Prevention Class A) ($P<.001$) and to have a higher $CD4^+$% ($P<.001$), both at enrollment and at hospital discharge, than those who received antiretrovirals for treatment. Although viral loads were similar between the two groups at enrollment, women receiving prophylaxis had lower viral loads at hospital discharge

Table 1. Characteristics of Women in the Study Population, Overall and According to Country of Enrollment (N=770)

Characteristic	Country					
	Argentina (n=202)	Bahamas (n=35)	Brazil (n=502)	Mexico (n=31)	Total (n=770)	*P*
At enrollment						
Education (y)						
0–6	18 (9)	32 (91)	226 (45)	9 (29)	285 (37)	<.001
7–12	165 (82)	3 (9)	268 (53)	19 (61)	455 (59)	
13 or more	19 (9)	0 (0)	8 (2)	3 (10)	30 (4)	
Gainfully employed outside of the home						
Yes	33 (16)	18 (51)	113 (23)	4 (13)	168 (22)	.001
No	169 (84)	17 (49)	389 (77)	27 (87)	602 (78)	
Marital status						
Married, living with partner	170 (84)	13 (37)	367 (73)	19 (61)	569 (74)	<.001*
Divorced	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	
Separated	8 (4)	2 (6)	5 (1)	0 (0)	15 (2)	
Single	22 (11)	19 (54)	121 (24)	10 (32)	172 (22)	
Widowed	2 (1)	1 (3)	7 (1)	2 (6)	12 (2)	
Adjusted BMI						
Underweight	24 (12)	3 (9)	81 (16)	4 (14)	112 (15)	<.001†
Normal	126 (64)	9 (26)	307 (62)	20 (69)	462 (61)	
Overweight	29 (15)	5 (14)	56 (11)	3 (10)	93 (12)	
Obese	19 (10)	18 (51)	50 (10)	2 (7)	89 (12)	
Missing	4	0	8	2	14	
Tobacco use						
Yes	60 (30)	1 (3)	107 (21)	6 (19)	174 (23)	.001
No	142 (70)	34 (97)	395 (79)	25 (81)	596 (77)	
Cocaine use						
Yes	14 (7)	0 (0)	7 (1)	0 (0)	21 (3)	.002
No	188 (93)	35 (100)	495 (99)	31 (100)	749 (97)	
Parity						
0	41 (20)	8 (23)	119 (24)	4 (13)	172 (22)	.045
1	65 (32)	5 (14)	167 (33)	16 (52)	253 (33)	
More than 2	96 (48)	22 (63)	216 (43)	11 (35)	345 (45)	
Timing of enrollment						
First trimester	38 (19)	1 (3)	26 (5)	0 (0)	65 (8)	<.001‡
Second trimester	91 (45)	15 (43)	186 (37)	2 (6)	294 (38)	
Third trimester	71 (35)	19 (54)	278 (55)	28 (90)	396 (51)	
At delivery visit	2 (1)	0 (0)	12 (2)	1 (3)	15 (2)	
HIV clinical classification						
A	177 (88)	35 (100)	430 (86)	27 (87)	669 (87)	.017
B	6 (3)	0 (0)	33 (7)	4 (13)	43 (6)	
C (AIDS)	19 (9)	0 (0)	39 (8)	0 (0)	58 (8)	
Viral load (copies/mL)						
Less than 1,000	81 (40)	29 (83)	316 (65)	18 (62)	444 (59)	<.001
1,000 or more, less than 10,000	44 (22)	4 (11)	107 (22)	8 (28)	163 (22)	
10,000 or more	77 (38)	2 (6)	66 (14)	3 (10)	148 (20)	
Missing	0	0	13	2	15	
Receiving antiretrovirals at conception						
No	157 (78)	30 (86)	416 (83)	31 (100)	634 (83)	.006
Yes	45 (22)	5 (14)	83 (17)	0 (0)	133 (17)	
Unknown	0	0	3	0	3	
Receiving antiretrovirals at enrollment						
No	85 (42)	0 (0)	62 (12)	1 (3)	148 (19)	<.001
Yes	117 (58)	35 (100)	440 (88)	30 (97)	622 (81)	

(*continued*)

(*P*=.049). Women who received antiretrovirals for prophylaxis tended to only receive one antiretroviral regimen during pregnancy (87%), whereas women who received antiretrovirals for treatment were more likely to receive more than one regimen (27%) (*P*<.001). Also, women receiving antiretrovirals for

Table 1. Characteristics of Women in the Study Population, Overall and According to Country of Enrollment (N=770) (*continued*)

Characteristic	Country					
	Argentina (n=202)	Bahamas (n=35)	Brazil (n=502)	Mexico (n=31)	Total (N=770)	*P*
During pregnancy						
Number of antiretroviral regimens received during pregnancy for 28 days or more						
1	149 (74)	35 (100)	391 (78)	25 (81)	600 (78)	.007§
2	34 (17)	0 (0)	81 (16)	3 (10)	118 (15)	
3	7 (3)	0 (0)	6 (1)	0 (0)	13 (2)	
4	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	
None, or antiretrovirals not received for 28 days or more	12 (6)	0 (0)	23 (5)	3 (10)	38 (5)	
Most complex antiretroviral regimen received during pregnancy for 28 days or more						
1 NRTI	7 (4)	0 (0)	41 (8)	0 (0)	48 (6)	<.001‖
2 NRTIs	35 (17)	0 (0)	6 (1)	17 (55)	58 (8)	
2 NRTIs plus 1 NNRTI	99 (49)	35 (100)	122 (24)	3 (10)	259 (34)	
2 NRTIs plus 1 PI	44 (22)	0 (0)	306 (61)	8 (26)	358 (46)	
Other	5 (3)	0 (0)	4 (1)	0 (0)	9 (1)	
None, or antiretrovirals not received for 28 days or more	12 (6)	0 (0)	23 (5)	3 (10)	38 (5)	
Reason for receipt of antiretrovirals during pregnancy						
Prophylaxis	96 (51)	22 (65)	287 (58)	11 (37)	416 (56)	.039
Treatment	91 (49)	12 (35)	204 (42)	19 (63)	326 (44)	
Missing	15	1	11	1	28	
At delivery visit or hospital discharge						
Mode of delivery						
Vaginal	85 (42)	24 (69)	206 (41)	1 (3)	316 (41)	<.001
Elective cesarean delivery	73 (36)	5 (14)	196 (39)	19 (61)	293 (38)	
Other cesarean delivery	42 (21)	6 (17)	99 (20)	11 (35)	158 (21)	
Missing	2	0	1	0	3	
Duration of ruptured membranes						
Less than 4 h	105 (86)	14 (58)	148 (65)	4 (80)	271 (72)	<.001
4 h or more	17 (14)	10 (42)	78 (35)	1 (20)	106 (28)	
Missing	80	11	276	26	393	
HIV clinical classification						
A	177 (88)	35 (100)	428 (85)	27 (87)	667 (87)	.013
B	6 (3)	0 (0)	35 (7)	4 (13)	45 (6)	
C (AIDS)	19 (9)	0 (0)	39 (8)	0 (0)	58 (7)	
Viral load (copies/mL)						
Less than 1,000	166 (86)	25 (81)	377 (82)	14 (48)	582 (82)	<.001
1,000 or more, less than 10,000	21 (11)	4 (13)	49 (11)	9 (31)	83 (12)	
10,000 or more	6 (3)	2 (6)	32 (7)	6 (21)	46 (6)	
Missing	9	4	44	2	59	
At 6–12 weeks postpartum						
HIV clinical classification						
A	177 (88)	35 (100)	426 (85)	27 (87)	665 (86)	.010
B	6 (3)	0 (0)	37 (7)	4 (13)	47 (6)	
C (AIDS)	19 (9)	0 (0)	39 (8)	0 (0)	58 (8)	

BMI, body mass index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NRTI, nucleoside or nucleotide analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Data are n (%).

* *P* value calculated for married, living with partner compared with others.

† *P* value calculated for underweight compared with normal compared with overweight or obese

‡ *P* value calculated for first or second trimester enrollment compared with third trimester compared with at labor and delivery

§ *P* value calculated for none, or antiretrovirals not received for 28 days or more, compared with one regimen compared with two or more regimens.

‖ *P* value calculated for 1 or 2 NRTIs compared with 2NRTIs+1PI compared with 2NRTIs+1NNRTI

prophylaxis were more likely to receive one or two nucleoside or nucleotide analogue reverse transcriptase inhibitors as the most complex regimen during pregnancy than women who received antiretrovirals for treatment ($P<.001$). Finally, mode of delivery varied significantly according to the reason for receipt

of antiretrovirals during pregnancy (P=.009), with women receiving prophylaxis more likely to deliver vaginally.

Maternal HIV disease stage at enrollment, whether assessed clinically or by laboratory measures (viral load or CD4$^+$%), was not associated with mode of delivery. Although the most complex regimen received during pregnancy did not vary by mode of delivery, those women who delivered by cesarean section were more likely to have received two or more antiretroviral regimens during pregnancy (P<.001) and were more likely to have received antiretrovirals for treatment (P=.009). At hospital discharge after delivery, only viral load (P<.001), and not clinical classification or CD4$^+$%, varied significantly by mode of delivery (with women who delivered by cesarean section being more likely to have a viral load of 1,000 copies/mL or more). In this study population, 38% of women delivered by elective cesarean delivery and, among those with a viral load less than 1,000 copies/mL at hospital discharge, 35% had undergone delivery by elective cesarean delivery.

Three characteristics at enrollment were associated with a viral load of 1,000 copies/mL or more at hospital discharge after delivery: a lower CD4$^+$% (P<.001), a viral load of 1,000 copies/mL or more(P<.001), and receipt of antiretrovirals (P=.018). Country of enrollment (P<.001) and lack of receipt of antiretrovirals during pregnancy also was associated with a viral load of 1,000 copies/mL or more at hospital discharge (P=.023). In addition, the mode of delivery was associated with the viral load at hospital discharge after delivery (10% of women who delivered vaginally had a viral load of 1,000 copies/mL or more compared with 25% of women with elective cesarean delivery and 20% other cesarean delivery) (P<.001). Finally, the most complex antiretroviral regimen received during pregnancy for 28 days or more (specifically, a regimen containing two nucleoside or nucleotide analogue reverse transcriptase inhibitors and one nonnucleoside reverse transcriptase inhibitor was inversely associated with a viral load of 1,000 copies/mL or more (P=.002). Timing of enrollment (P=.073), receiving antiretrovirals at conception (P=.080), and reason for receipt of antiretrovirals during pregnancy (P=.070) did not have statistically significant associations with the outcome of interest. In multivariable logistic regression analyses (Table 2), incorporating all 10 of these variables, timing of enrollment (third trimester or at delivery), receipt of antiretrovirals at conception, low CD4% at enrollment, high viral load at enrollment, and country of enrollment were associated with a viral load of 1,000 copies/mL or more. The most complex antiretroviral

Table 2. Multivariable Analysis of Factors Associated With Maternal Viral Load of 1,000 Copies/mL or More at Hospital Discharge After Delivery (n=618)

Characteristic	Adjusted Odds Ratio	95% CI
Timing of enrollment		
First or second trimester	1 (reference)	–
Third trimester or delivery visit	1.80	1.09–2.97
Receiving antiretroviral(s) at conception		
No	1 (reference)	–
Yes	2.26	1.28–4.00
Viral load (copies/mL) at enrollment		
Less than 1,000	1 (reference)	–
1,000 or more	3.30	2.04–5.36
CD4+ lymphocyte percent at enrollment		
Less than 15%	1.76	0.80–3.84
15% or more, less than 25%	1.84	1.13–3.00
25% or more	1 (reference)	–
Country of enrollment		
Brazil	1 (reference)	–
Argentina	0.62	0.35–1.10
Bahamas	2.55	0.85–7.64
Mexico	4.58	1.82–11.49
Most complex antiretroviral regimen received during pregnancy for 28 days or more		
None, or antiretrovirals not received for 28 days or more	3.39	1.25–9.20
1 NRTI or 2 NRTIs	1.99	0.89–4.47
2 NRTIs plus 1 PI	2.12	1.18–3.82
2 NRTIs plus 1 NNRTI	1 (reference)	–

CI, confidence interval; NRTI, nucleoside or nucleotide analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

regimen received for 28 days or more during pregnancy (2 nucleoside or nucleotide analogue reverse transcriptase inhibitors and 1 nonnucleoside reverse transcriptase inhibitor) was inversely associated with a viral load of 1000 copies/mL or more.

Of the 770 infants in the study population, none were breastfed and all received antiretroviral prophylaxis. Infant low birth weight (yes or no), preterm birth (yes or no), and gender did not vary significantly according to maternal country of residence. Thirteen percent of infants were low birth weight, and 9% were preterm. The median birth weight for the overall study population was 3,000 g, and ranged from 2,900 to 3,300 g across countries ($P<.001$). The median gestational age for the overall study population was 39 weeks, and ranged from 38–39 weeks across countries ($P<.001$).

Of the 770 infants, seven have been diagnosed with HIV infection (0.91% [95% confidence interval 0.37–1.86]). Several factors were evaluated for possible associations with mother-to-child transmission of HIV, including maternal factors (country, HIV clinical classification, viral load, and $CD4^+$% at enrollment and at hospital discharge after delivery; adjusted BMI at enrollment; timing of enrollment into the NICHD International Site Development Initiative study; receipt of antiretrovirals at conception and at enrollment; receipt of antiretrovirals during pregnancy; reason for receipt of antiretrovirals during pregnancy, most complex antiretroviral regimen received for 28 days or more during pregnancy, and number of antiretroviral regimens received during pregnancy; mode of delivery; duration of ruptured membranes); and infant factors (infant birth weight, gestational age, and gender). With three exceptions, none of these factors had statistically significant associations with infant HIV infection status. Infants whose mothers were not receiving antiretrovirals at the time of enrollment into the NICHD International Site Development Initiative protocol were more likely to be infected than those whose mothers were receiving antiretrovirals at enrollment ($P=.026$). Infants whose mothers had a $CD4^+$% below 25% at hospital discharge after delivery ($P=.017$) were also more likely to be infected. Low birth weight was associated with mother-to-child transmission of HIV, with 43% of those infected being low birth weight compared with only 13% of those uninfected ($P=.049$). Due to the very small number of HIV-infected infants, multivariable analyses were not pursued.

DISCUSSION

In this relatively healthy population of HIV-infected pregnant women receiving care at clinical centers in Latin America and the Caribbean, virtually all women (99%) received antiretrovirals during pregnancy. Of these, most (56%) received antiretrovirals for mother-to-child transmission prophylaxis. Most women who received antiretrovirals received a three-drug regimen (84%). Almost equal proportions of women delivered vaginally (41%) or by cesarean before labor and before ruptured membranes (38%). Only a minority of women (18%) had a viral load of 1,000 copies/mL or more at hospital discharge after delivery. This outcome was associated with disease stage (more advanced) at enrollment, enrollment late in pregnancy, and receipt of antiretrovirals at conception and inversely associated with the most complex antiretroviral regimen received during pregnancy (two nucleoside or nucleotide analogue reverse transcriptase inhibitors and one nonnucleoside reverse transcriptase inhibitor). None of the infants were breastfed, and all received antiretroviral prophylaxis. The rate of mother-to-child transmission of HIV was extremely low, and was associated with maternal HIV disease management and immunologic status around the time of delivery and with infant birth weight.

Because this was an observational protocol, the clinical care provided to all women and infants enrolled in the NICHD International Site Development Initiative Perinatal Study is independent of the research protocol. As expected, women who were healthier at enrollment (less symptomatic, with a higher $CD4^+$%) were more likely to receive antiretrovirals for prophylaxis than for treatment. Similarly, women who received antiretroviral prophylaxis during pregnancy received fewer regimens (usually only one). Women who received antiretrovirals for prophylaxis were more likely to have (as the most complex antiretroviral regimen during pregnancy of 28 days duration or more) a regimen containing only one or two nucleoside or nucleotide analogue reverse transcriptase inhibitors (22%). In contrast, only 4% of women who received antiretrovirals for treatment received regimens containing one or two nucleoside or nucleotide analogue reverse transcriptase inhibitors. Based on evidence that (even among pregnant women who do not meet criteria for treatment) receipt of more potent antiretroviral regimens is associated with a lower risk of transmission, it has been recommended in general that HIV-infected pregnant women receive combination regimens of three antiretrovirals.[2,11,12]

Subsequent to the demonstration of the efficacy and effectiveness of elective cesarean delivery for prevention of mother-to-child transmission of HIV,[13,14] cesarean delivery as a preventive intervention has been recommended for certain pregnant, HIV-infected women.[2,11,12] Brazilian and U.S. guidelines recommend elective cesarean delivery for women not receiving antiretrovirals and for women with an unknown plasma viral load or a viral load of 1,000 copies/mL or more; it is recommended that women with a viral load of less than 1,000 copies/mL deliver vaginally.[2,11] In addition, the most recent Brazilian guidelines recommend the use of zidovudine alone and offering of elective cesarean delivery for women diagnosed with HIV infection relatively late in pregnancy (at 37 weeks or more of gestation) and who are asymptomatic with higher total lymphocyte count and hemoglobin results.[12] In this study population, 38% of women delivered by elective cesarean delivery and, among those with a viral load of less then 1,000 copies/mL at hospital discharge, 35% had undergone delivery by elective cesarean delivery.

As expected, women with a viral load of 1,000 copies/mL or more at hospital discharge after delivery were more likely to have had more advanced HIV disease at enrollment (eg, with a lower $CD4^+$% and a higher viral load). However, antiretroviral management during pregnancy also was associated with achieving this outcome, and women with higher viral loads were more likely to be delivered by elective cesarean delivery.

Those women who were not receiving antiretrovirals at enrollment and who had a lower $CD4^+$% at the time of delivery were more likely to transmit HIV to their infants, and infant low birth weight was associated with mother-to-child transmission of HIV. Low birth weight has been associated with mother-to-child transmission of HIV,[15–18] although whether low birth weight infants are at higher risk of acquiring HIV infection once exposed to the virus, or whether acquisition of HIV infection in utero leads to low birth weight remains controversial. In a previous review of all eight cases of mother-to-child transmission of HIV in this cohort to date (including both singletons and twins), we found that 62% of cases of mother-to-child transmission were missed opportunities for prevention (eg, inadequate antiretroviral prophylaxis) (D'Ippolito M, Read JS, Rocha N, Mussi-Pinhata M, Korelitz J. Missed opportunities for prevention of mother-to-child transmission of HIV-1 in Latin America and the Caribbean: The NICHD International Site Development Initiative (NISDI) Perinatal Study. Ped Infect Dis J. In press). However, a large proportion of cases (38%) were those in which the medical and surgical management seemed appropriate, emphasizing the importance of continued research regarding mechanisms of and interventions to prevent mother-to-child transmission of HIV.

In summary, in this relatively healthy population of HIV-infected pregnant women receiving care at clinical centers in Latin America and the Caribbean, only a minority of women had a viral load of 1,000 copies/mL or more around the time of delivery, and the rate of mother-to-child transmission of HIV was extremely low. In this study, virtually all women received antiretrovirals during pregnancy, whether for transmission prophylaxis or for treatment, and a large proportion of women delivered by elective cesarean delivery for prevention of mother-to-child transmission of HIV. Because of the demonstrated effectiveness of such prophylactic and treatment interventions, increasing numbers of HIV-infected women are being exposed to antiretrovirals during pregnancy and are undergoing elective cesarean delivery for prevention of transmission. Analyses of adverse events related to treatment of HIV disease in pregnant women and interventions for the prevention of transmission in this study population are underway.

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APPENDIX: INTERNATIONAL SITE DEVELOPMENT INITIATIVE PERINATAL PROTOCOL

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